BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2001 (31.05.2001)

PCT

(10) International Publication Number
WO 01/37811 A1

(51) International Patent Classification[7]: A61K 9/20, 9/00, A61P 33/00

(21) International Application Number: PCT/EP99/08979

(22) International Filing Date:
22 November 1999 (22.11.1999)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **AKZO NOBEL N.V.** [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HURON, Sébastien** [FR/FR]; Castex Village, F-09350 Daumazan (FR). **LACOSTE, Eric** [FR/FR]; Lamonzie Saint Martin, F-24680 Monbouché (FR).

(74) Agent: **VAN GENT, Marieke**; Patent Dept Pharma, N.V. Organon, NL-5340 BH Oss (DE).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/37811 A1

(54) Title: COMPOSITION ALLOWING PREDEFINED AND CONTROLLED RELEASE OF ACTIVE INGREDIENT, PREPARATION THEREOF AND USE

(57) Abstract: A new composition is disclosed which is especially designed for combatting external and internal parasitoses. In one embodiment this composition contains, as an active ingredient, an endectocide, the form of a subcutaneous implant constituted by one or more pellets that release the active ingredient in a predetermined and controlled way. In specific embodiments the endectocide is an avermectin or a milbemicin, in particular ivermectin.

Description

COMPOSITION ALLOWING PREDEFINED AND CONTROLLED RELEASE OF ACTIVE INGREDIENT. PREPARATION THEREOF AND USE

FIELD OF THE INVENTION

The present invention relates to a composition, preferably to a pharmaceutical composition containing an active ingredient, such as antiparasitics, which is capable to become administered to, preferably implanted subcutaneously into an organism, such as an animal, and to release said active ingredient in a predefined and controlled manner.

DESCRIPTION OF THE PRIOR ART

Various ways of administration of acitve ingredients to an organism are knwon, e.g. via the oral route (per os) through tablets, capsules, liquids (suspensions or solutions), drops, syrup and slow release bolus. Tor animals the administration of liquids, powder, paste, granules via the animal feed or drinking water is often used.

The parenteral application [e.g. subcutaneous (s.c.), intramuscular (i.m.), intraperitoneal (i.p.), intraveneous (i.V.)] can occur e.g. per injection, infusion or implantation.

Another option is the local (topical) aplication which can be made by using a spray, bath, dip, ointment, liquid suspension or solution, cream or pour-on.

The treatment of various diseases requires the maintenance of a sufficient level of pharmaceutically active ingredients in certain body fluids over a defined period.

One example is the control of infectious diseases with antibiotics that require a defined concentration of the antiinfective ingredient in the body fluids where the pathogen is located to kill the pathogens or control the bacteria replication. Another example is the control of parasites in and on the organism.

On the other hand the pre-determination of an optimal and convenient treatment regime is considered as a further positive effect. Especially in the prophylactic and therapeutic treatment of animals with pharmacologically active substances additional handling of animals that can lead to stress, body weight loss and labour effors for the farmers can be reduced.

This effect can be reached through a composition allowing predefined and controlled release of an active ingredient. Some of the known principle ways of adminstration are applicable for a controlled relase of an active ingredient to an organism.

Examples are fomulations, known as „long acting injectable formulations", „slow release bolus" and also subcutaneous implants.

But as of today there are only a few formulations available in the art which allow release of an active ingredient in a predetermined and controlled manner to an organism. Thus, there is a continued need for formulations allowing active ingredients to become administered to an organism, such as implanted subcutaneously and releasing said active ingredients in a predetermined and controlled manner, such as over a prolonged amount of time.

Formulations that are administered as s.c. implants are known per se. But as of today the known formulations are generally produced via extrusion of their components or via microencapsulation. Both methods are costly and the production method can cause loss of activity in thermo-sensitive components or may contain residues of solvents used in the production process. The loss of activity in thermo-sensitve conponents does not allow the use of this method with thermolabile active ingredients. The residues of solvents may lead to side-

effects following the administration to the organism. Thus there is a continued need for improved subcutaneous implant and an improved production method for such a formulation.

Whereas the compositions of this invention can become administered to any kind of organism, such as humans and animals, preferably mammals, the invention will be described in more detail via the treatment of animals with pharmaceutically active substances, especially antiparasitics.

One indication, which is economically important in agriculture, is the use of pre-defined and controlled release of pharmaceutically active ingredients in the control of parasites in livestock ruminants (e.g. cattle, sheep and goat).

Parasites can be classified into Endoparasites and Ectoparasites. Endoparasites, for example worms (nematodes), cestodes and trematodes are hosted inside (e.g. gastrointestinal tract, respiratory tract) the organism (human or animal). Ectoparasites, for example fleas, mites, ticks and lice are hosted on (on or in the skin) the organism (human or animal).

Active ingredients are known that control Endoparasites (Endoparasitics, e.g. Fenbendazol, Pyrantel, Praziquantel) or Ectoparasities (Ectoparasitics, e.g. Deltamethrin, Fipronil, Lufenuron) and active ingredients that control both Endoparasites and Ectoparasites (Endectoparasitics, e.g. Abamectin, Ivermectin, Milbemycin, Cydectin).

These active ingredients can be adminstered in various formulation, e.g. as powder, spray, pour-on, bath, dip, injection, tablets, bolus or suspension.

For an effective control of the parasite in or on the animal the following facts are especially important; species and stage of the parasite as well as species, age, breed and sex, body weight and condition of the host animal. Therefore it is for an effective control of parasites important to have a formulation available that allows an individual dosage of the active ingredient.

On the other hand the administration of antiparasitics to animals, especially ruminante is a very labour intensive work and causes stress and loss of body weight of the animals. It woud be

therefore desirable to have a formulation available that allows pre-defined and controlled release of a prolonged time period.

But as of today only a few formulations are available in the art that allow the pre-defined and controlled release of antiparasitics to animals that allow individual dosage and an be manufactured cost effectively.

Consequently, there was a need for a formulation meeting these requirements, and the present inventor took on the task of creating and providing such a formulation.

Another object of the present invention is an improved manufacturing process for such products minimizing or avoiding the risk of thermo-degradation of the components of such product and/or minimizing or avoiding the content of residual solvents from the manufacturing process in the product.

Another object of the present invention is an easy to handle manufacturing process for such products using equipment that is common in the manufacturing of other parmaceutical formulations thus minimizing the cost of such manufacture.

Still another object of the present invention is the provision of implants with dosages of active ingredients being individually adaptable to the needs of the specific prophylactic or therapeutic treatment. Current products use a fixed dosage in the implants. Individual dosages are especially desired for animal treatment with regard to different species, body weight, breed and age.

BRIEF DESCRIPTION OF THE INVENTION

The present invention meets these requirements, by providing a composition, preferably a pharmaceutical composition for predefined and controlled release of an active ingredient.

The present invention relates to a composition allowing a predefined and controlled release of an active ingredient to an organism when administered to said organism, which composition comprises a combination A) of at least two components

a) at least one active ingredient in dispersed solid form,

b) at least one gelling agent,

c) optionally at least one filler, and

d) optionally at least one adjuvant

which combination A) is in the form of discrete particles and is embedded into a matrix B) which is formed by a pore-forming agent and optionally at least one adjuvant.

The composition of this invention can be administered to an organism in various ways known to those skilled in the art. Preferred is the form of an implant, preferably a subcutaneous implant.

The composition of this invention preferably contains, as an active ingredient, an endectocide in the form of subcutaneous implants, constituted by one or more tablets that release the active ingredient in a predetermined and controlled manner during a period quite longer as known formulations allow, of up to about 1 year, preferably of about 4 months, thus reducing the labor costs, the movement of the animals, the losses of body weight and of production of milk due to such movements, besides protecting the animals and their hide against the attack of the parasites.

DETAILED DESCRIPTION OF THE INVENTION

The duration of the action of the composition of the invention can be easily controlled by manipulating the concentration of the active principle and of the excipients.

As an active ingredient a) in dispersed solid form any active substance can be used that is desired to become released when administered to an organism.

Active ingredients can be all types of biologically active substances, preferably pharmaceutically active substances.

Examples of biologically active substances are antibiotics, antiparasitics, hormones, growth promotors, anti-cancer drugs, vitamines and vaccines.

More specific examples of pharmaceutically active substances are BST, trenbolone, zeranol, ivermectin, abamectin, doramectin, moxidectin, selamectin and other systemical compounds.

More than one active ingredient can be used, for example a synergistic combination of two pharmaceutically active ingredients.

Thus, a composition according to the present invention can also additionally contain other biologically active agents used in human or veterinary medicine such as, for example, vaccines, antibiotics, growth promoters, agents that potentialize the antiparasite effect of the active ingredient or that improve or avoid its side effects.

Preferably the active ingredient is an endectocide, especially preferred an avermectin or a milbemicin and most especially preferred ivermectin and abamectin.

When administering an endectocide to an animal, effective treatment and control of the different species of pulmonary and gastrointestinal round worms, ticks, myiases (known as "bicheiras"), larvae of Dermatobia hominis, lice, mites of mange and of the fly known as "mosca-dos-chifres" is possible.

The active ingredient is solid and is applied in dispersed form, for example in the form of powder or preferred in the form of granules. Solid shall mean solid at 25°C.

The gelling agent b) can be of any kind as long as this agent is physiologically acceptable and forms together a gel or a shapable mass with component a), with optional components c) and d) and with a liquid, for example water or body fluids.

Examples of gelling agents are organic or inorganic gelling agents, such as modified cellulose, modified starch, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylates, polymethacrylates, or

dispersed silica. Preferred is modified cellulose, preferably alkylated cellulose, most preferred ethylcellulose.

The filler c) can be of any kind as long as this is a pharmacologically inactive substance. Examples of filler c) are carbohydrates and silica, preferably a disaccharide, and most preferred lactose.

The matrix material B) embedding shaped particles from components a), b), optionally c) and optionally d) is a pore-forming agent. This agent is soluble in body fluids and after being administered to the organism this agent dissolves thereby forming pores in the matrix. Thus the body fluids become access to the combination A) comprising components a), b) and optionally c) and d) and the active ingredient is released in a predetermined and controlled manner. Examples of pore-forming agents are polyalkylene ethers, polyvinyl alcohol, sugar and sugar alcohols. Examples for sugars are lactose, glucose and preferred saccarose. Examples for sugar alcohols are mannitol and sorbitol.

Preferred as pore-forming agents are polyalkylene ethers or polyvinyl alcohol. Said polyalkylene ethers or polyvinylalcohols are available in different aggregate forms, depending on their molecular weight, as liquids or solids at 25°C. For use in the instant invention the polyalkylene ethers and the polyvinylalcohols should be matrix-forming and shapable via compression methods. The molecular weight of the pore-forming agent should be selected adequately to allow pore-forming effects in contact with body fluids.

Examples of polyalkylene ethers are polybutylene ethers, polypropylene ethers or especially polyethylene ethers. Preferably a nonionic polymer of polyethylene oxide, a polyethylene glycol, a polyethyleneglycol alkyl ether or combinations thereof are used. Said matrix material B) in addition can contain one or more adjuvants d).

Most preferred as a material forming matrix B) is a a nonionic polymer of polyethylene oxide possessing a molecular weight (weight average) between 3M and 10 M, whereby M stands for a million.

A very preferred matrix material B) for use in the instant invention is the excipient Polyox® from Union Carbide Corporation; this being a nonionic polymer of polyethylene oxide with specifications of USP-NF 1990. In this respect reference is made to the leaflet of Union Carbide Corporation published in the USA in 1994 under the title "POLYOXYO WATER-SOLUBLE RESINS FOR PHARMACEUTICALS", incorporated herein by reference. The molecular weight of Polyox used in the implants of the present invention is of 4 M, 5 M and 7 M, where M stands for 1 million.

In the compositions of the present invention one can use all the forms of Polyox mentioned in said leaflet, as well as other different forms of excipients that can be used for the same purpose as Polyox, such as polyethylene glycol, polyethylene glycol alkyl ether, polyvinyl alcohol, other derivatives of polyoxyethylene and other polymers usable for the same purpose.

In a preferred form the composition of this invention is in the form of a tablet. But other forms are also applicable, for example rods, capsules, microparticles and granules.

Besides components a), b) and optionally c) the compositions of the instant invention may contain additional adjuvants known in the art of formulations. Examples of such adjuvants are carrier materials, such as starch, starch derivatives, talc, stearic acid or salts thereof, fats, waxes, natural or hardened oils; liquids, such as water, alcohols, e.g. ethanol, glycerin, or polyols; vegetable oils; polymers or copolymers, such as copolymers from glycolic acid and lactic acid; fillers; binders; lubricants; surfactants; stabilizers, emulsifiers; disperging agents; thinners; thickening agents; solvents; preservation agents; buffer agents; salts; and antioxidants.

Such adjuvants can be contained in the component A) and/or in the component B) of the composition of this invention.

The amount of components a), b), c) and d) in composition A) can generally be varied in a broad range.

Typical amounts of component a) are 0.01 – 98 % by weight, preferred 20 - 95 % by weight and most preferred 35 - 85 % by weight.

Typical amounts of component b) are 0.01 – 20 % by weight, preferred 0.1 – 10 % by weight and most preferred 0.5 – 5 % by weight.

Typical amounts of component c) are 0 – 60 % by weight and preferred 1 – 40 % by weight.

Typical amounts of component d) are 0 – 10 % by weight and preferred 0 – 5 % by weight. The indicated amounts for components a), b), c) and d) refer to the total of said components in a composition.

The weight proportion of combination A) and matrix material B) can also be varied in a broad range. Typical amounts of matrix material B) are 2 – 50 % by weight, preferably 5 – 40 % by weight, referred to the total composition of A) and B).

The compositions of the instant invention can be prepared by mixing components a), b), optionally c) and optionally d) in a conventional mixing equipment. This can be performed in dry form or under addition of a liquid, preferably water. The mass thus formed should be shapable to form a plurality of small pieces, such as grains, of component A). The formation of such small pieces can be performed by conventional shaping means, for example by pressing the obtained mass through a mesh. The obtained small pieces are then combined with the matrix forming component or components. This can be performed in conventional mixing equipment. After the combination of components A) and B) is performed, this composition is given the final shape in a shaping equipment for said combination of components A) and B). Examples thereof are a pelletizer, an extruder or preferably a tablet press.

Thus the instant invention also relates to a process of manufacturing the above defined composition said process encompassing the measures:

i) combining components a), b), optionally c) and optionally d) in a mixing equipment,

ii) mixing said components together with a liquid to form a shapable mass A)

iii) shaping said mass A) into a plurality of small pieces by applying a first shaping means to said mass A) and separating said mass A) into a plurality of small pieces;

iv) combining said small pieces of mass A) with a pore-forming agent B) and optionally with at least one adjuvant d);

v) mixing said combination of components A) and B) to form a shapable composition; and

vi) shaping said composition to a desired shape by means of a second shaping means.

In a preferred process of this invention a tablet press is used as a shaping means. In this process the application of heat and/or organic solvents can be avoided and easily available equipment can be used.

The shaped composition, for example tablets, obtained according to this process can be combined to form an implant.

In a convenient form of presentation of the implants of the present invention, they are packed in plastic cartridges containing a plurality of implants, which are usable for treating of several animals.

An implant is in general constituted by a certain number of tablets, for instance 5, 10, or 15 tablets. These tablets are called "pellets".

A more specific formulation according to the present invention and containing the Endectoparasitics Ivermectin as an active ingredient typically contains approximately the following:

- active ingredient: 9 - 20 mg/pellet
- Polyox : 10 - 30% (weight/weight)

- Lactose: 20 - 50% (weight/weight)
- Talc: 6 - 10% (weight/weight)
- Magnesium Stearate: 1 % (weight/weight)
- Ethyl Cellulose N200: 1 % (weight/weight)

resulting in a total weight of 30 mg/pellet.

In veterinary applications the implant is preferably applied to the ear of the animal, since this region has sufficient blood vessels, thus permitting a desired absorption of the active ingredient.

As an example for the pharmacokinetics of an active ingredient from the compositions of this invention, the specific product Ivermectin, after being absorbed, gets into the bloodstream, deposits on the fat and is distributed by the secretions into the bloodstream, the digestive apparatus, respiratory apparatus, liver, and is eliminated by the feces and urine.

The compositions of this invention can be applied to any organism where predetermined and controlled release of an active ingredient is desired, especially where individual dosage is required. Examples of organisms are vertebrates and non-vertebrates. Preferred is the application to humans and animals.

EXAMPLE OF MANUFACTURE OF THE PELLETS USABLE IN ACCORDANCE WITH THE PRESENT INVENTION

In order to prepare a batch of pellets, the following procedure was applied:

1) On the day before, a gel is prepared with ethylcellulose and alcohol in the following proportions:

- ethyl alcohol: 0.7 l
- ethylcellulose N200: 0.045 kg

Leave in a stirrer for 30 minutes until the lumps are eliminated. Cover the excipient in order to avoid evaporation of alcohol and leave it standing overnight.

2) In a GUEDU-type mixer, incorporate ivermectin and lactose.

Cover and mix it for 5 minutes at maximum speed.

Add the gel, under motion, during 1.30 minutes.

Leave the mixer on for 1 minute more.

3) Add absolute alcohol (0.05 l) previously passed in the container that contained the gel (washed from the container).

4) If necessary, complete with (absolute) ethyl alcohol (0.2 - 0.25 l).

Leave the GUEDU mixer in motion at top speed until a very fine granulate is obtained.

5) Pass the granulate through 1.60mm mesh and put it on a stainless steel tray (5), forming a regular layer on each tray.

6) Dry in a vacuum oven at room temperature for 2h30min.

Pass the dried granulate through 3 trays of 1.6mm mesh and 2 trays of 1.0 mm mesh.

Leave it dry in a vacuum oven at ambient temperature until the next day.

7) Repeat the screening by passing it through 3 trays of 1.6 mm mesh and 2 trays of 1.0 mm mesh.

Put the material in a GUEDU mixer. Add talc and Polyox, stir and add the magnesium stearate. Perform the mixing action and transfer to obtained mixtures to a tablet press and produce tablets.

Typical characteristics:

- diameter - 3 mm
- shape - cylindrical
- approximate weight - 30 mg
- thickness - 3.3 - 3.7 mm

EXAMPLES OF THE FORMULATION OF PELLETS USABLE IN IMPLANTS ACCORDING TO THE PRESENT INVENTION.

Following the procedure described in the preceding EXAMPLE OF MANUFACTURE and using the amounts of the various ingredients respectively indicated, pellets of the compositions given below in examples 1 - 16 were obtained, that were usable to release a sufficient level of ivermectin over a certain period.

Example 1

Pellets containing 18.38 mg of ivermectin/pellet and 10% of Polyox 301:

Ivermectin:	136.0 g
Polyox 301:	20.0 g
Lactose:	42.0 g
Talc:	8.0 g
Magnesium stearate:	2.0 g
Ethylcellulose:	2.0 g
To result in a total of:	210.0 g

Example 2

Pellets containing 14.28 mg of ivermectin/pellet and 10% of Polyox 301:

Ivermectin:	99.3 g
Polyox 301:	19.0 g
Lactose:	63.8 g
Talc:	11.9 g
Magnesium stearate:	1.9 g
Ethylcellulose 200:	1.46 g
To result in a total of:	197.4 g

Example 3

Pellets containing 9.70 mg of ivermectin/pellet and 10% g of Polyox 301:

Ivermectin:	72.48g
Polyox 301:	20.2 g
Lactose:	100.6 g
Talc:	15.7 g
Magnesium stearate:	2.0 g
Ethylcellulose 200:	1.06 g
To result in a total of:	212.1 g

Example 4

Pellets containing 19.30 mg of ivermectin/pellet and 10% of Polyox Coag:

Ivermectin:	136.00 g
Polyox Coag:	20.2 g
Lactose:	32.0 g
Talc:	8.0 g
Magnesium stearate:	2.0 g
Ethylcellulose 200:	2.0 g
To result in a total of:	200.0 g

Example 5

Pellets containing 15.0 mg of ivermectin/pellet and 10% of Polyox Coag:

Ivermectin:	122.94 g
Polyox Coag:	23.3 g
Lactose:	72.96 g
Talc:	9.3 g
Magnesium stearate:	2.3 g
Ethylcellulose 200:	1.8 g
To result in a total of:	232.6 g

Example 6

Pellets containing 10.40 mg of ivermectin/pellet and 10% of Polyox Coag:

Ivermectin:	91.75 g
Polyox Coag:	25.0 g
Lactose:	119.7 g
Talc:	10.0 g
Magnesium stearate:	2.5 g
Ethylcellulose 200:	1.3 g
To result in a total of:	250.4 g

Example 7

Pellets containing 19,30 mg of ivermectin/pellet and 10% of Polyox 303:

Ivermectin:	136.0 g
Polyox 303:	20.0 g
Lactose:	32.0 g
Talc:	8.0 g
Magnesium stearate:	2.0 g
Ethylcellulose 200:	2.0 g
To result in a total of:	200.0 g

Example 8

Pellets containing 15.00 mg of ivermectin/pellet and 10% of Polyox 303:

Ivermectin:	147.5 g
Polyox 303:	25.1 g
Lactose:	63. g
Talc:	10.0 g
Magnesium stearate:	2.5 g
Ethylcellulose 200:	2.5 g
To result in a total of:	250.6 g

Example 9

Pellets containing 10,40 mg of ivermectin/pellet and 10% of Polyox 303:

Ivermectin:	136.0 g
Polyox 303:	20.0 g
Lactose:	32.0 g
Talc:	8.0 g
Magnesium stearate:	2.0 g
Ethylcellulose 200:	2.0 g
To result in a total of:	200.0 g

Example 10

Pellets containing 18.60 mg of ivermectin/pellet and 30% of Polyox 301:

Ivermectin:	130.5 g
Polyox 301:	57.5 g
Lactose:	3.3 g
Talc:	4.0 g
Magnesium stearate:	1.9 g
Ethylcellulose 200:	1.9 g

To result in a total of: 199.1 g

Example 11

Pellets containging 14.84 mg of ivermectin/pellet and 30% of Polyox 301:

Ivermectin:	90.3 g
Polyox 301:	51.9 g
Lactose:	20.6 g
Talc:	6.89 g
Magnesium stearate:	1.7 g
Ethylcellulose 200:	1.3 g

To result in a total of: 172.6 g

Example12

Pellets containing 10.31 mg of ivermectin/pellet and 30% of Polyox 301:

Ivermectin:	54.90 g
Polyox 301:	45.6 g
Lactose:	43.2 g
Talc:	5.2 g
Magnesium stearate:	1.5 g
Ethylcellulose 200:	0.8 g

To result in a total of: 151.2 g

Example 13

Pellets containing 18,60 mg of ivermectin/pellet and 30% of Polyox Coag:

Ivermectin:	130.46 g
Polyox Coag:	57.5 g
Lactose:	3.3 g
Talc:	4.0 g

Magnesium stearate:	1.9 g
Ethylcellulose 200:	1.9 g
To result in a total of:	199.1 g

Example 14

Pellets containing 14.80 mg of ivermectin/pellet and 30% of Polyox Coag:

Ivermectin:	91.03 g
Polyox Coag:	52.0 g
Lactose:	24.3 g
Talc:	4.3 g
Magnesium stearate:	1.7 g
Ethylcellulose 200:	1.3 g
To result in a total of:	174.5 g

Example 15

Pellets containing 10,31 mg of ivermectin/pellet and 30% of Polyox Coag:

Ivermectin:	61.62 g
Polyox Coag:	50.8 g
Lactose:	49.8 g
Talc:	4.9 g
Magnesium stearate:	1.7 g
Ethylcellulose 200:	0.9 g
To result in a total of:	169.6 g

Example 16

Pellets containing 18,60 mg of ivermectin/pellet and 30% of Polyox 303:

Ivermectin:	130.46 g

Polyox 303:	57.5 g
Lactose:	3.3 g
Talc:	4.0 g
Magnesium stearate:	1.9 g
Ethylcellulose 200:	1.9 g
To result in a total of:	199.1 g

Example 17

Pellets containing 14.64 mg of ivermectin/pellet and 30% of Polyox 303:

Ivermectin:	83.17 g
Polyox 303:	47.3 g
Lactose:	22.1 g
Talc:	6.2 g
Magnesium stearate:	1.6 g
Ethylcellulose 200:	1.2 g
To result in a total of:	161.3 g

Example 18

Pellets containing 10,40 mg of ivermectin/pellet and 30% of Polyox 303:

Ivermectin:	57.46 g
Polyox 303:	47.5 g
Lactose:	46.9 g
Talc:	6.2 g
Magnesium stearate:	1.6 g
Ethylcellulose 200:	0,8 g
To result in a total of:	160.5 g

CLAIMS

1. A composition allowing a predefined and controlled release of an active ingredient to an organism when administered to said organism, which composition comprises a combination A) of at least two components
   a) at least one active ingredient in dispersed solid form,
   b) at least one gelling agent,
   c) optionally at least one filler, and
   d) optionally at least one adjuvant

   which combination A) is in the form of discrete particles and is embedded into a matrix B) which is formed by a pore-forming agent and optionally at least one adjuvant.

2. A composition according to claim 1 wherein the active ingredient is a pharmaceutically active substance.

3. A composition according to claim 1 wherein the active ingredient is selected from the group consisting of antibiotics, antiparasitics, hormons, growth promoters, anti-cancer drugs, vitamines and vaccines.

4. A composition according to claim 2 wherein the pharmaceutically active substance is an antiparasitics, preferably an endectocide, and most preferably an avermectin or a milbemicin.

5. A composition according to claim 3 or 4 wherein the avermectin is ivermectin and/or abamectin.

6. A composition for combatting external and internal parasitoses according to claim 1, which contains an endectocide as an active ingredient and which is in the form of a subcutaneous implant constituted by one or more pellets that release the active ingredient in a controlled and prolonged way.

7. A composition according to claim 1 wherein the gelling agent is selcted from the group consisting of modified cellulose, modified starch, pectin, polyvinyl alcohol, polyvinyl pyrrolidone and dispersed silica or combinations thereof.

8. A composition according to claim 7 wherein the modified cellulose is an alkylated cellulose, preferably ethylcellulose.

9. A composition according to claim 1 wherein the filler is selected from the group consisting of carbohydrates and silica or combinations thereof.

10. A composition according to claim 9 wherein the carbohydrate is a disaccharide, preferably lactose.

11. A composition according to claim 1 wherein the pore-forming agent forming matrix B) is selected from the group consisting of polyethylene ether, polyvinyl alcohol, sugar, sugar alcohol or combinations thereof.

12. A composition according to claim 1 wherein the polyethylene ether is a nonionic polymer of polyethylene oxide, a polyethylene glycol or a polyethyleneglycol alkyl ether

13. A composition according to claim 1 wherein the composition is in the form of a pellet.

14. A composition according to claim 13 wherein an implant is constituted by a plurality of such pellets.

15. A composition according to claim 14 wherein said implants are packed in plastic cartridges.

16. A process of manufacturing the composition of claim 1 said process encompassing the measures:

i) combining components a), b), optionally c) and optionally d) according to claim 1 in a mixing equipment,

ii) mixing said components together with a liquid to form a shapable mass A)

iii) shaping said mass A) into a plurality of small pieces by applying a first shaping means to said mass A) and separating said mass A) into a plurality of small pieces;

iv) combining said small pieces of mass A) with pore-forming agent B) and optionally with at least one adjuvant d);

v) mixing said combination of components A) and B) to form a shapable composition; and

vi) shaping said composition to a desired shape by means of a second shaping means.

17. A process according to claim 16 wherein said second shaping means is a tablet press.

18. A method of treating an organism with an active ingredient in a predetermined and controlled manner said method comprises administering to said organism a composition according to claim 1.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 99/08979

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/00 A61P33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 458 887 A (CHEN CHIH-MING ET AL) 17 October 1995 (1995-10-17) column 2, line 20 - line 31 column 2, line 54 - line 56 claims 1-7,13,14; examples ---	1,2,7, 11-13, 16-18
X	US 5 472 708 A (CHEN CHIH-MING) 5 December 1995 (1995-12-05) column 1, line 61 - last line column 2, line 33 - line 41 column 2, line 60 -column 3, line 4 claims; examples --- -/--	1,2,7,8, 16-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2000	31/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 99/08979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 42 30 563 A (BOEHRINGER INGELHEIM KG) 17 March 1994 (1994-03-17) page 2, line 1 - line 5 page 2, line 28 - line 34 page 3, line 14 - line 22 examples A,B; table 1 claims 1-12 page 2, line 14 - line 16	1,2, 9-12, 16-18
X	WO 87 02240 A (HAESSLE AB) 23 April 1987 (1987-04-23) page 3, line 16 -page 4, line 26; claims 1,6,7,10; example 9	1-3,7-9, 11,18
X	WO 89 00045 A (RIKER LABORATORIES INC) 12 January 1989 (1989-01-12) page 4, line 21 - line 31 page 6, line 35 -page 7, last line; claims 1,7; examples	1,2,7,8, 12,13,18
A	WO 99 15166 A (HUATAN HIEP ;PFIZER LTD (GB); PFIZER (US)) 1 April 1999 (1999-04-01) page 1, line 1 - line 5 page 3, line 1 - line 19 page 6, line 1 - line 23 claims; example 4	1-18

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]ional Application No
PCT/EP 99/08979

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5458887	A	17-10-1995	NONE		
US 5472708	A	05-12-1995	US	5260069 A	09-11-1993
			AU	680642 B	07-08-1997
			AU	5549294 A	22-06-1994
			CA	2149152 A	09-06-1994
			EP	0670718 A	13-09-1995
			JP	8506802 T	23-07-1996
			NZ	258012 A	28-10-1996
			WO	9412160 A	09-06-1994
DE 4230563	A	17-03-1994	NONE		
WO 8702240	A	23-04-1987	SE	450087 B	09-06-1987
			AT	62409 T	15-04-1991
			AU	593038 B	01-02-1990
			AU	6529686 A	05-05-1987
			CA	1293449 A	24-12-1991
			CN	1025283 B	06-07-1994
			CS	8607294 A	14-08-1989
			CY	1764 A	15-07-1994
			DD	266734 A	12-04-1989
			DE	3678729 D	16-05-1991
			DK	287687 A	04-06-1987
			EP	0277127 A	10-08-1988
			ES	2003139 A	16-10-1988
			FI	881657 A,B,	08-04-1988
			GR	862526 A	09-02-1987
			HK	11494 A	18-02-1994
			HU	47843 A,B	28-04-1989
			IE	58967 B	01-12-1993
			JP	2560019 B	04-12-1996
			JP	63501080 T	21-04-1988
			KR	9400098 B	05-01-1994
			LT	2310 R	15-12-1993
			LV	5394 A	10-03-1994
			LV	5750 A	20-12-1996
			LV	5827 A	20-01-1998
			NO	175514 B	18-07-1994
			NZ	217697 A	26-04-1989
			PH	24739 A	01-10-1990
			PT	83508 A,B	01-11-1986
			SE	8504720 A	12-04-1987
			SG	8094 G	15-04-1994
			SU	1706373 A	15-01-1992
			US	5246714 A	21-09-1993
			US	4927640 A	22-05-1990
			ZA	8606861 A	27-05-1987
WO 8900045	A	12-01-1989	DE	3721574 A	12-01-1989
			AU	2124588 A	30-01-1989
			EP	0370049 A	30-05-1990
			NZ	225158 A	21-12-1990
			ZA	8804622 A	28-02-1990
WO 9915166	A	01-04-1999	AU	9742298 A	12-04-1999
			EP	1014970 A	05-07-2000